HIV exposed uninfected South African infants experience greater severity but not frequency of common infectious diseases than HIV unexposed uninfected infants

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**Introduction**

- **HIV exposed uninfected (HEU) infants in Africa may experience greater infectious morbidity than HIV unexposed uninfected (HUU) infants**

- **HEU infant infectious morbidity pathways**
  
  **Universal infant risk factors:**
  - Infant feeding, maternal mortality, poverty, preterm birth/small for gestational age, infectious pathogen exposure

  **HEU-unique exposures:**
  - HIV viral particle exposure, maternal immune compromise, ARVs

Maternal HIV → HEU Infant → Infectious Morbidity

Universal Factors:
- Maternal mortality
- Poverty
- Preterm / Small for gestation
- Pathogen exposure

HEU-unique Factors:
- HIV particle exposure
- Maternal immune compromise
- Antiretroviral drug exposure
Infectious morbidity severity

- ZVITAMBO (N = 12 000+) & Mashi (N = 671)
  - greater relative difference in mortality than hospitalization

- Pneumonia treatment response at 48 hours
  - KZN (N = 116) & Botswana (N = 217)
  - HEU infants greater odds of empiric treatment failure

- Drakenstein Child Health Study (N= 697)
  - All pneumonia aRR 1.6 (95% CI 1.0, 2.6) HEU
  - Severe pneumonia aRR 4.0 (95% CI 1.5, 10.8) HEU

Marinda 2007, Koyanagi 2011; Shapiro 2007; McNally 2007; Kelly 2014; Le Roux 2015
Objectives

Primary:

To determine whether HIV exposed uninfected (HEU) infants have a greater probability of infectious cause hospitalization or death in the first 6 months of life, compared to HIV unexposed uninfected (HUU) infants from a single community, after controlling for differences in infant feeding.

Secondary:

To determine whether HEU infants have a greater probability of severe or very severe infectious cause hospitalization or death than HUU infants.
Definitions

Determinants

• Primary: HIV exposure (HEU / HUU)
  – Maternal HIV-infection status confirmed on all mothers at 2 weeks postnatal
  – Infant HIV-infection excluded at 6 weeks (HEU) and 6 months (HEU & HUU)

• Secondary: breastfeeding
  – Any / none at 2 weeks or 6 months

Outcomes

• Primary: at least 1 infectious cause hospitalization or death
• Secondary: at least 1 severe or very severe infectious cause hospitalization or death

• Study specific case-definitions:
  – Type and grade (mild-moderate, severe, very severe)
  – Based on WHO IMCI & SA child health management guidelines
Study Design & Setting

• Prospective cohort study in Kraaifontein, South Africa
• HIV-infected and uninfected mothers & their newborns
• Midwife obstetric unit – low risk term deliveries
• Enrolled July 2012 to June 2013
• Followed-up to 6 months
  – 4 visits
Control for **confounding** in study design

- **Socio-economic circumstances**
  - 4 well-defined low socio-economic neighbourhoods

- **Maternal habits – alcohol, smoking, drug use**
  - Mothers frequency matched on race/ethnicity

- **Maternal health**
  - Low risk obstetric histories
  - No major medical comorbidities

- **Birth outcomes**
  - > 36 weeks gestation, > 2000g

- **Seasonality of common childhood infections**
  - HEU and HUU infants matched within 30 days of birth
Outcome Determination

• Linkage with provincial electronic hospital administration system and mortality registry
  – Identify occurrence of hospitalization or death
  – All infants including those lost to face-to-face follow-up

• Hospital record abstraction according to a standardized abstraction source document, excluding all HIV exposure information

• 2 paediatricians independently graded and classified all hospitalization events according to the study-specific case-definitions
Results

Delivery: 264 mother-infant pairs
(136 HIV exposed, 128 HIV unexposed)

2 weeks: 176 (67%) mother-infant pairs
(94 HEU infants, 82 HUU infants)

6 months: 134 (76%) mother-infant pairs
(75 HEU infants, 59 HUU infants)
Maternal Characteristics

• Demographic
  – HIV-infected mothers significantly older than HIV-uninfected mothers (median 27.8 vs. 24.7 years, p<0.008)
  – No difference in race, marital status, education, income

• Obstetric
  – Equivalent antenatal care received
  – No major obstetric morbidities

• Health
  – Similar postnatal BMI (median 26.6 vs. 26.5 kg/m²)
  – Delivery CD4 count lower in HIV-infected than HIV-uninfected mothers (343 cells/μl vs. 467 cells/μl, p <0.001)
Infant Characteristics

• **No difference** between HEU and HUU infants in
  – Birth weight (mean 3118g vs. 3231g, p = 0.07)
  – Gestational age (mean 38.7 vs. 39.1 weeks, p = 0.06)
  – Immunization up take (93% vs. 91% complete at 6 months)

• Fewer HEU infants breastfed than HUU infants
  – Never breastfed: two thirds of HEU, 1 HUU infant
  – 6 months: 85% of HEU and 32% of HUU not breastfeeding

• Breastfed infants
  – median duration 112 days (IQR 56, 194)
  – no difference between HEU and HUU
Sick clinic visit rates

No difference in sick clinic visit rates
Primary Outcome Events

- 27 infants had a primary outcome event
  - 17 HEU infants hospitalized once
  - 10 HUU infants (8 hospitalized once, 1 hospitalized twice, 1 death)

- 18% of HEU and 12% of HUU

- Unadjusted risk ratio
  1.48 (95% CI 0.72, 3.06)
## Infectious Cause Hospitalizations

<table>
<thead>
<tr>
<th></th>
<th>Total (N=176)</th>
<th>HEU (N=94)</th>
<th>HUU (N=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-moderate (%)</td>
<td>3 (1.7)</td>
<td>2 (2.1)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Severe (%)</td>
<td>9 (5.1)</td>
<td>5 (5.3)</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>Very severe (%)</td>
<td>14 (8.0)</td>
<td>10 (10.6)</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory (%)</td>
<td>17 (9.7)</td>
<td>10 (10.06)</td>
<td>7 (8.5)</td>
</tr>
<tr>
<td>Diarrhea* (%)</td>
<td>9 (5.1)</td>
<td>8 (8.5)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Other# (%)</td>
<td>5 (2.8)</td>
<td>4 (4.3)</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

*P = 0.04

*Other events: 3 HEU presumed neonatal sepsis, 1 HEU post-neonatal *Shigella sonnei* septicemia, 1 HUU uncomplicated neonatal conjunctivitis
The effect of HIV exposure on infectious morbidity

At least one infectious cause hospitalization or death in HEU relative to HUU infants

(adjusted for maternal age and any breastfeeding at 6 months)

<table>
<thead>
<tr>
<th></th>
<th>aOR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>All</td>
<td>1.47</td>
<td>0.54, 4.25</td>
</tr>
<tr>
<td>Severe</td>
<td>1.31</td>
<td>0.45, 4.02</td>
</tr>
<tr>
<td>Very severe</td>
<td>1.37</td>
<td>0.39, 5.57</td>
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</table>
Stratified Analysis: No breastfeeding

2 weeks

Models not possible
(single HUU infant not breastfed at 2 weeks)

6 months

<table>
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<tr>
<th>Outcome</th>
<th>aOR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>All</td>
<td>1.34</td>
<td>0.42, 5.19</td>
</tr>
<tr>
<td>Severe</td>
<td>1.06</td>
<td>0.32, 4.18</td>
</tr>
<tr>
<td>Very severe</td>
<td>1.04</td>
<td>0.27, 5.09</td>
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All models adjusted for maternal age
### Stratified Analysis: Any breastfeeding

#### 2 weeks

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<tr>
<th>Outcome</th>
<th>aOR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>All</td>
<td>1.96</td>
<td>0.59, 6.22</td>
</tr>
<tr>
<td>Severe</td>
<td>2.16</td>
<td>0.64, 7.01</td>
</tr>
<tr>
<td>Very severe</td>
<td>4.21</td>
<td>1.00, 19.22</td>
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#### 6 months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>aOR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>All</td>
<td>1.82</td>
<td>0.24, 10.2</td>
</tr>
<tr>
<td>Severe</td>
<td>2.07</td>
<td>0.27, 12.0</td>
</tr>
<tr>
<td>Very severe</td>
<td>3.75</td>
<td>0.14, 6.00</td>
</tr>
</tbody>
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All models adjusted for maternal age
Summary

- In term infants born to mothers without major obstetric or medical morbidities, in similar socioeconomic and household circumstances and with an equivalent frequency of infant sick-clinic visits

  - There is no evidence of a difference in infectious morbidity comparing HEU and HUU infants that stop breastfeeding before 6 months of age

  - Breastfed HEU infants vs. breastfed HUU infants had a 4 X greater probability of very severe infectious morbidity
Limitations

• Sample size & attrition
• Residual confounding by infant feeding and socioeconomic circumstances

Strengths

• Appropriate HIV unexposed comparison group
• Outcome severity grading
Conclusion

• HEU and HUU infants may differ in the severity but not in the incidence of common childhood infections experienced

• HEU-unique exposures may mediate some of the risk of HEU infant infectious morbidity
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